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Robert A. Yokel

*University of Kentucky*, [ryokel@email.uky.edu](mailto:ryokel@email.uky.edu)

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# Aluminum in Food – The Nature and Contribution of Food Additives

Robert A. Yokel

*Pharmaceutical Sciences, University of Kentucky  
USA*

## 1. Introduction

Aluminum (Al) is distributed throughout the environment because of its presence as the third most abundant element on earth. Concern about Al toxicity to humans, including from food sources, has persisted since the demonstration that it has the potential to be a neurotoxicant (Wiley 1928, 1929; Schaeffer et al. 1928; Döllken 1898; Gies 1911; Anon. 1913; Yokel and Golub 1997; WHO 1997; Krewski et al. 2007; ATSDR 2008). Exposure of humans to Al is mainly from food, water, airborne dust, antiperspirants, immunizations, allergy injections and antacids (Table 1). Foods and beverages are the single largest contributor of Al intake for the typical human, providing ~ 3.5 to 10 mg/day. Food additives provide a significant percentage of the daily intake. Among the food additives, sodium aluminum phosphates (SALPs) are the main contributors. Drinking water provides ~ 0.1 mg. Other sources for some humans, their daily exposures and intakes, estimated percentage absorbed, and amount of Al that enters the blood are summarized in Table 1. The history of the use and regulation of Al food additives in the US, approved Al-containing food additives in the US and some other countries, primary food types contributing Al to the diet, typical daily dietary Al intake, dietary intake in relation to established tolerable intake and minimal risk levels, and some discussion of Al absorption, distribution, excretion, and toxicity are presented in this chapter.

Aluminum is present in food naturally, as a food additive, and taken up through contact with Al used in food preparation and storage. The Al content of foods is highly variable, depending upon the food product, its processing or lack thereof, the site of growth of the food stuff, and for grains if they are Al-tolerant varieties. Contamination of food with soil, that typically contains 5 to 10% Al, can significantly increase the Al content of the food, although the Al may not be in a readily absorbable form.

## 2. The history of aluminum-containing food additives in the US

Smith (1928) reviewed the Report of the Referee Board of Consulting Scientific Experts, Created by Executive Order of President Roosevelt in February, 1908, to address the safety of the use of Al compounds in food. He also reviewed the published literature and some unpublished studies up to 1925 and court cases relevant to the use of Al in baking powders and conducted some studies himself. He concluded, in agreement with the Referee Board created by President Roosevelt and the court ruling in *State of Missouri vs. Whitney Layton*,

Source	Al concentration	Daily Al exposure	Estimated percentage absorbed	Al absorbed daily ( $\mu\text{g/kg}$ ) <sup>a</sup>
<i>Typical Exposures</i>				
Water	Average $\sim 70 \mu\text{g/l}$	100 $\mu\text{g}$	0.3 <sup>b</sup>	0.004
Food - total diet		3500-10,000 $\mu\text{g}$ <sup>c</sup>	0.1 to 0.3 <sup>d</sup>	0.05-0.4
Air-office	0.15 $\mu\text{g}/\text{m}^3$ <sup>e</sup>	1 $\mu\text{g}$	1 to 2 from lungs <sup>f</sup> 0.1 to 0.3 from GI tract	0.0002 0.00003
Air-outside	0.2 - 1 $\mu\text{g}/\text{m}^3$ <sup>e,g</sup>	4 $\mu\text{g}$ <sup>h</sup>	1 to 2 from lungs <sup>f</sup> 0.1 to 0.3 from GI tract	0.001 0.0001
Antiperspirants	5-7.5% <sup>i</sup>	50,000-75,000 $\mu\text{g}$	up to 0.012 <sup>j</sup>	up to 0.1
Vaccines, pediatric patient	125-330 $\mu\text{g}/\text{dose}$	1.4 $\mu\text{g}$ <sup>k</sup>	100 eventually <sup>l</sup>	0.07
<i>Elevated Exposures</i>				
Antacids/phosphate Binders		up to 5,000,000 $\mu\text{g}$	0.1	80
Industrial Air	25-2500 $\mu\text{g}/\text{m}^3$	250-25,000 $\mu\text{g}$ per work day	1 to 2 from lungs <sup>f</sup> 0.1 to 0.3 from GI tract	0.6-8 0.008-1
Allergy immunotherapy	150-850 $\mu\text{g}/\text{dose}$	7-40 $\mu\text{g}$ <sup>m</sup>	100 eventually <sup>l</sup>	0.1-0.6
Dialysis solution	If tap water 50 $\mu\text{g}/\text{l}$	2400 $\mu\text{g}$	25 <sup>n</sup>	9
Total Parenteral Nutrition Solutions	Neonatal/pediatric	9-23 $\mu\text{g}/\text{kg}$ <sup>o</sup>	100	9-23
	Adult	1.5 $\mu\text{g}/\text{kg}$ <sup>p</sup>	100	1.5

<sup>a</sup>Based on a 70 kg adult except for vaccines (20 kg child) and total parenteral nutrition solutions. <sup>b</sup>(Yokel et al. 2001a; Zhou, Harris, and Yokel 2008; Stauber et al. 1999; Priest et al. 1998). <sup>c</sup>Based on reports cited in the text. <sup>d</sup>(Stauber et al. 1999; Yokel and Florence 2006; Yokel, Hicks, and Florence 2008). <sup>e</sup>(Horemans et al. 2008). <sup>f</sup>Based on Al exposure in an industrial setting: (Sjögren et al. 1997; Gitelman et al. 1995; Pierre et al. 1995; Riihimäki et al. 2000; Priest 2004). <sup>g</sup>(Jones and Bennett 1986). <sup>h</sup>(Priest 2004). <sup>i</sup>Based on 20% Al zirconium glycine complex or 25% Al chlorohydrate in a topical product, which are typical concentrations (POISINDEX information system, Micromedex, Inc, Englewood, CO). <sup>j</sup>Based on (Flarend et al. 2001), assuming that the percentage of Al absorbed does not change with repeated exposure. <sup>k</sup>Based on 30 injections in the first 6 years of life, an average weight of 20 kg, 0.75 mg from RECOMBIVAX HB®, 1.32 mg from Pentacel®, 0.5 mg from Prevnar®, 0.5 mg from HAVRIX® and none from RotaTeq®, Fluzone®, M-M-R® II, or Varivax®, assuming absorption over 6 years. <sup>l</sup>(Flarend et al. 1997). <sup>m</sup>Based on a typical allergen extract treatment schedule and maintenance injections for 3.5 years of one allergen extract. <sup>n</sup>(Kovalchik et al. 1978). <sup>o</sup>(Speerhas and Seidner 2007; Poole et al. 2010; Bohrer et al. 2010). <sup>p</sup>(Speerhas and Seidner 2007).

Table 1. Sources of Al exposure, Al concentration in the source, resultant daily Al exposure from the source, estimated percentage absorbed from the source, and calculated amount of Al absorbed daily, normalized to body weight. Modified from (Yokel and McNamara 2001)

1899, that baking powder containing sodium aluminum sulfate had not been shown to cause functional disorders or disease or impairment of the digestion and general health to humans.

Al salts were used in food prior to 1958. The U.S. Congress amended the Food, Drug and Cosmetic Act (FDC Act) in 1958 (Food Additives Amendment) to require pre-market approval of any substance intentionally added to food, that becomes a component of food or otherwise affects the characteristics of food, unless the use of the substance is generally recognized as safe (GRAS) or otherwise excepted from the definition of food additive, e.g., a color additive. A temporal summary of the development of food regulation in the US is available at:

(<http://www.fda.gov/Food/FoodIngredientsPackaging/GenerallyRecognizedasSafeGRAS/ucm094040.htm>). It legislated exemptions for many substances with a history of safe use as food. For substances used in foods prior to 1958, the FDA permits expert opinion to be based on a reasoned judgment founded in experience with common food use, taking into account reasonably anticipated patterns of consumption, cumulative effects in the diet, and safety factors appropriate for the utilization of animal experimentation data. Appropriate regulation is also required that is published in the Federal Register and codified in the Code of Federal Regulations (CFR). The food additive petition process of the FDA is based on Section 409 of the FDC Act. Corresponding regulations are described in CFR Title 21. The GRAS substance list appears in 21 CFR Parts 171, 182, 184, and 186. These regulations are accessible on the Internet, e.g., 21 CFR 133.169 at: <http://frwebgate.access.gpo.gov/cgi-bin/get-cfr.cgi?TITLE=21&PART=133&SECTION=169&TYPE=TEXT>.

In 1959 the US FDA published a list of substances it considered to be GRAS for use in foods. GRAS is defined in CFR 121.1. Legal authority for Al as GRAS is codified in 21 CFR 182. The list included Al salts. Food additive approval does not require human clinical testing and there is no risk-benefit analysis. GRAS recognition may be based on scientific procedures (safety studies) or through experience based on common use in food prior to 1958. The original determination of GRAS status of Al was based on common use. President Nixon in 1969 directed the FDA to undertake a systematic safety review of all GRAS substances. The Life Sciences Research Office (LSRO) of the Federation of American Societies for Experimental Biology (FASEB) was contracted by the FDA to review and evaluate the available information on each GRAS substance, summarize the available scientific literature, and to recommend what restrictions, if any, on their use would be needed to ensure their safe use in food. A re-review of the GRAS status of Al was conducted by a select committee of the FASEB in 1975, Select Committee on GRAS Substances [SCOGS]. It was based on the previous review, a review of the published literature from 1920 to 1973 related to the safety of Al compounds as food ingredients (Tracor-Jitco 1973), and unpublished studies contracted by producers of SALP which was fed to rats and dogs. The opinion of the select committee was that "There is no evidence in the available literature on ...acidic sodium aluminum phosphate [and other Al forms] ... that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when they are used at levels that are now current or that might reasonably be expected in the future" (FASEB 1975) (<http://www.fda.gov/Food/FoodIngredientsPackaging/GenerallyRecognizedasSafeGRAS/GRASSubstancesSCOGSDatabase/default.htm>). Although noting that care should be taken by patients with kidney disease when consuming food containing high levels of Al salts, the authors did not mention dialysis encephalopathy, which has been attributed to Al, or the

controversial role of Al in Alzheimer's disease. Description of these clinical problems began about the same time (Crapper, Krishnan, and Dalton 1973; Alfrey, LeGendre, and Kaehny 1976).

In 1982 the FDA issued Toxicological Principles for the "Safety Assessment of Direct Food Additives and Color Additives Used in Food" (a.k.a. the Red Book) to provide testing guidelines to obtain scientific evidence of safety (Humphreys 1992). In 1992 the FDA was in the process of reviewing Al, which was evidently not completed. The FDA Center for Food Safety and Applied Nutrition is responsible for monitoring Al in foods, that which is naturally occurring, and that which is from food additives (Pennington 1992).

### **3. The current approved uses, purposes for use, and regulation of aluminum-containing food additives**

#### **3.1 In the US**

Aluminum is used as a direct food additive as a firming agent, carrier, coloring agent, anticaking agent, buffer, neutralizing agent, dough strengthener, emulsifying agent, stabilizer, thickener, leavening agent, curing agent and texturizer. Direct food additives are those that have been intentionally added to food for a functional purpose, up to a few %. These additives are used in milk, processed cheese, yogurt, preserves, jams and jellies, baking soda, sugars, cereals, flours, grains and powdered or crystalline desert products (Pennington 1987). Table 2 lists FDA-approved GRAS food additives containing Al and Table 3 other FDA-approved Al-containing food additives.

The most important uses include the addition of acidic SALP to self-rising flour as an acidifying and leavening agent; basic SALP to processed cheese, cheese food and cheese spread as an emulsifying agent to give them a soft texture and easy melting characteristics (Lione 1983); and sodium aluminosilicate as an anticaking agent. Acidic SALP  $\text{NaAl}_3\text{H}_{14}(\text{PO}_4)_8 \cdot 4\text{H}_2\text{O}$  reacts with  $\text{NaHCO}_3$  to produce the leavening action by generating  $\text{CO}_2$ . Basic SALP  $(\text{Na}_8\text{Al}_2(\text{OH})_2((\text{PO})_4)_4)$  is one of many "emulsifying salts" added to process cheese, cheese food and cheese spread which react with and change the protein of cheese to produce a smooth, uniform film around each fat droplet to prevent separation and bleeding of fat from the cheese. This produces the desired soft texture of cheese, easy melting characteristics, and desirable slicing properties (Ellinger 1972).

Aluminum is also permitted in lakes (water-soluble artificial colors adsorbed onto alumina), which typically have an Al content of 25% (United Kingdom Ministry of Agriculture Fisheries and Food 1993). Alumina (Al oxide) is the only substratum approved for manufacturing U.S. Food, Drug & Cosmetic approved lakes (Soni et al. 2001). These are listed in Table 3.

Aluminum and some Al compounds are also approved by the FDA as indirect food additives (21CFR) Parts 175, 176, 177, and 178. Indirect food additives are substances used in food-contact articles, and include adhesives and components of coatings (Part 175), paper and paperboard components (Part 176), polymers (Part 177), and adjuvants and production aids (Part 178). In general, these are substances that may come into contact with food and enter food products in small quantities as a result of growing, processing or packaging (<http://www.fda.gov/Food/FoodIngredientsPackaging/ucm115333.htm>).

- Prior-sanctioned food ingredients. Stabilizers (substances that may migrate from food-packaging material into food) (21 CFR 181.29)
  - Aluminum mono-, di-, and tristearate
- GRAS substances (21 CFR 182)
  - Substances migrating to food from paper and paperboard products (182.90)
    - Alum (double sulfate of aluminum, and ammonium, potassium, or sodium)
    - Aluminum hydroxide
    - Aluminum oleate [1975, 43,1]
    - Aluminum palmitate [1975, 43,1]
    - Sodium aluminate, [1975, 43,1]
    - Sodium phosphoaluminate, [1975, 43,1]
  - Multiple purpose GRAS food substances (Subpart B)
    - Aluminum sulfate (182.1125), [1975, 43,1]
    - Aluminum ammonium sulfate (182.1127), [1975, 43,1], buffer and neutralizing agent
    - Aluminum potassium sulfate (182.1129 ), [1975, 43,1], buffer and neutralizing agent
    - Aluminum sodium sulfate (182.1131), [1975, 43,1], buffer and neutralizing agent
    - Sodium aluminum phosphate, acidic (182.1781), [1975, 43,1] a leavening agent in cereal foods and related products, self-rising flours & meals
    - Sodium aluminum phosphate, basic (182.1781), [1975, 43,1] an emulsifying agent in pasteurized process cheese, cheese food and cheese spread
  - Anticaking Agents (Subpart C)
    - Aluminum calcium silicate, (182.2122), [1979,1], anticaking agent, < 2% by weight in table salt; (169.179), vanilla powder
    - Sodium aluminosilicate (sodium silicoaluminate) (182.2727), [1979,61,1], anticaking agent, < 2%
    - Sodium calcium aluminosilicate, hydrated (sodium calcium silicoaluminate) (182.2729), [1979,61,1], anticaking agent, < 2%
- Direct food substances affirmed as GRAS (21 CFR 184)
  - Aluminum hydroxide (184.1139) [1975, 43,1]
- Indirect food substances affirmed as GRAS (21 CFR 186)
  - Clay (kaolin), which consists of hydrated aluminum silicate (186.1256)

SCOGS conclusion:

1. There is no evidence in the available information on [substance] that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when they are used at levels that are now current or might reasonably be expected in the future.

Table 2. Generally recognized as safe (GRAS) food additives containing Al. The 21 CFR for those substances that have a CFR citation is in parentheses. The year of the SGOGS review report, the report number, and its conclusion are in brackets

- Cheeses and related cheese products
  - To bleach milk for cheese, potassium alum, (133.102, 106, 111, 141, 165, 181, 183, and 195), < 0.012%
  - Grated cheeses: Sodium aluminosilicate
  - Pasteurized process cheese: sodium aluminum phosphate, (133.169), < 3% by weight
  - Pasteurized process cheese food, sodium aluminum phosphate, (133.173), < 3% by weight
  - Pasteurized process cheese spread, sodium aluminum phosphate, (133.179), < 3% by weight
- Cereal flours and related products, Subpart B
  - Flour: potassium alum and sodium aluminum sulfate, (137.105)
  - Self-rising flour: sodium aluminum phosphate (137.180)
  - Self-rising white corn meal: sodium aluminum phosphate (137.270)
- Eggs and egg products
  - Dried whole eggs and egg yolks: sodium silicoaluminate, anticaking agent, (160.105), < 2%
  - Food dressings and flavorings
  - Vanilla powder: Aluminum calcium silicate, (169.179), < 2%
- Food additives permitted for direct addition to food for human consumption, Subpart D—Special Dietary and Nutritional Additives
  - As a source of niacin in foods for special dietary use, aluminum nicotinate, dietary supplement, (172.310)
  - Salts of fatty acids: aluminum salts of fatty acids, binder, emulsifier, and anticaking agent (172.863)
  - Food starch-modified: aluminum sulfate, [1979,115,3], (172.892), < 2.0%
- Defoaming agents: Secondary direct food additives permitted in food for human consumption
  - Aluminum stearate - Processing beet sugar & yeast, antifoaming (or defoaming) agent, (173.340)
- Boiler water additives, in steam contacting food
  - Sodium aluminate, (173.310)
- Aluminum in lakes
  - FD&C Blue #1 aluminum lake
  - FD&C Blue #2 aluminum lake on alumina
  - FD&C Red #40 aluminum lake
  - FD&C Yellow #5 aluminum lake
- Indirect food additives: adjuvants, production aids, and sanitizers, Subpart B - Substances utilized to control the growth of microorganisms, coatings on fresh citrus fruit
  - Aluminum
  - Aluminum acetate
  - Aluminum di(2-ethylhexoate)

Table 3. (continues on next page) Some other FDA-approved sources of Al in food



- Aluminum distearate
- Aluminum, hydroxybis[2,4,8,10-tetrakis(1,1-dimethylethyl)-6-hydroxy12h-ibenzoid[d,g][1,3,2]dioxaphosphocin 6-oxidato]
- Aluminum isodecanoate
- Aluminum linoleate
- Aluminum monostearate
- Aluminum naphthenate
- Aluminum neodecanoate
- Aluminum oxide
- Aluminum potassium silicate
- Aluminum ricinoleate
- Aluminum silicate
- Aluminum sodium sulfate, anhydrous
- Aluminum stearoyl benzoyl hydroxide
- Bis(benzoate-o)(2-propanolato)aluminum
- D&C Red no. 7-aluminum lake
- Dialkyldimethylammonium aluminum silicate
- Gum rosin, aluminum salt
- Gum rosin, disproportionated, aluminum salt
- Rosin, hydrogenated, aluminum salt
- Rosin, partially dimerized, aluminum salt
- Sodium aluminum pyrophosphate
- Soybean oil fatty acids, aluminum salt
- Tall oil fatty acids, aluminum salt
- Tall oil rosin, aluminum salt
- Tall oil rosin, disproportionated, aluminum salt
- Wood rosin, aluminum salt
- Wood rosin, disproportionated, aluminum salt

SCOGS conclusion:

3. While no evidence in the available information on [substance] demonstrates a hazard to the public when it is used at levels that are now current and in the manner now practiced, uncertainties exist requiring that additional studies be conducted.

Table 3. (continued) Some other FDA-approved sources of Al in food

### 3.2 Countries other than the US

Canada permits the use of Al as a food additive, as described in Part B Foods Division 16 of the Food and Drug Regulations of the Canadian Food and Drugs Act ([http://laws.justice.gc.ca/eng/regulations/C.R.C.,\\_c.\\_870/page-147.html#h-110](http://laws.justice.gc.ca/eng/regulations/C.R.C.,_c._870/page-147.html#h-110)). These regulations are similar to the FDA's. The fifteen member states of the European Union, as well as Norway and Iceland, allow the use of Al as a food additive. European Parliament and Council Directive 94/36/EC lays down detailed rules on colors and 95/2/EC, as amended by Directives 96/85/EC, 98/72/EC and 2001/5/EC, lays down detailed rules for authorization

of all food additives other than colors and sweeteners ([http://ec.europa.eu/food/fs/sfp/ flav\\_index\\_en.html](http://ec.europa.eu/food/fs/sfp/ flav_index_en.html)). Approved Al-containing food additives are shown in Table 4. The United Kingdom ([http://www.legislation.hmso.gov.uk/si/si1995/Uksi\\_19953187\\_en\\_5.htm#sdiv3](http://www.legislation.hmso.gov.uk/si/si1995/Uksi_19953187_en_5.htm#sdiv3)) and Australia and New Zealand (<http://www.foodstandards.gov.au/mediareleasespublications/publications/shoppersguide/foodadditivesnumeric1680.cfm>) also permit Al food additives. Regulations for the former are very similar to the EC's. The approved Al-containing food additives for the latter are shown in Table 5. Japan carries out food safety work under the Food Safety Basic Law (enacted in May 2003) and related laws

94/36/EC (colors):

- Aluminum metal (E 173) is authorized for the external coating of sugar confectionary and for the decoration of cakes and pastries.

95/2/EC:

- E520 Aluminum sulfate, firming agent
- E521 Aluminum sodium sulfate, firming agent
- E522 Aluminum potassium sulfate, acidity regulator
- E523 Aluminum ammonium sulfate, acidity regulator

(Aluminum sulfates (E 520-523) are permitted to be used in egg white up to 30 mg/kg; and candied, crystallized glacé fruit and vegetables, up to 200 mg/kg individually or in combination, expressed as aluminum

- E541 Sodium aluminum phosphate, acidic is permitted to be used in fine bakery wares (scones and sponge wares only) up to 1 g/kg expressed as aluminum.

[Sodium aluminum phosphate, basic is not authorized in the EU as a food additive]

- E554 Sodium aluminum silicate, anticaking agent
- E555 Potassium aluminum silicate, anticaking agent
- E556 Calcium aluminum silicate, anticaking agent
- E558 Bentonite (hydrated aluminum silicate), carrier in food colors, maximum 5%
- E559 Aluminum silicate (kaolin, anticaking agent)
- E554-E559 are permitted to be used in dried powdered foodstuffs (including sugars); salt and its substitutes; sliced or grated hard, semi-hard and processed cheese and sliced or grated cheese analogues and processed cheese analogues, up to 10 g/kg; chewing gum; rice; sausages as a surface treatment only; seasonings up to 30 g/kg; confectionery excluding chocolate as a surface treatment only; tin-greasing products up to 30 g/kg
- E1452 Starch aluminum octenylsuccinate, permitted encapsulated in vitamin preparations in food supplements in food supplements up to 35 g/kg

94/36/EC on colors for use in foodstuffs:

- Aluminum lakes of the permitted colors
- FD&C Red 40 aluminum lake (E 129)

Table 4. Allowed Al-containing additives for use in foodstuffs by the European Parliament and Council Directives

- Permitted flavoring substances, for the purposes of this Standard
  - Flavoring substances which are listed in at least one of the following publications:
    - Generally Recognized as Safe (GRAS) lists of flavoring substances published by the Flavour and Extract Manufacturers' Association of the United States from 1960 to 2011 (edition 25)
    - Chemically-defined flavoring substances, Council of Europe, November 2000
    - 21 CFR § 172.515
- 559 Aluminum silicate
- 470 Aluminum, calcium, sodium, magnesium, potassium and ammonium salts of fatty acids
- 556 Calcium aluminum silicate
- 554 Sodium aluminosilicate
- 470 Aluminum, calcium, sodium, magnesium, potassium and ammonium salts of fatty acids
- 541 Sodium aluminum phosphate, acidic (baking compound), [Basic SALP is not permitted as a food additive]
- 555 Potassium aluminum silicate, dried milk, milk powder, cream powder
- 555 Potassium aluminum silicate, cheese and cheese products up to 1%
- 173 Aluminum, confectioneries, spirits and liqueurs
- 556 Calcium aluminum silicate, salt

Table 5. Al-containing food additives permitted by the Australia New Zealand Food Standards Code - Standard 1.3.1. Colours and their aluminium and calcium lakes. A reference to a color listed in Schedules 1, 3 and 4 of this Standard includes a reference to the aluminum and calcium lakes prepared from that color

- Aluminum ammonium sulfate (ammonium alum), raising agent, processing aid
- Aluminum potassium sulfate (potassium alum), raising agent, processing aid
- Food Blue No. 1, aluminum lake, restricted for the purpose of coloring
- Food Blue No. 2, aluminum lake
- Food Green No. 3, aluminum lake
- Food Red No. 2, aluminum lake
- Food Red No. 3, aluminum lake
- Food Red No. 40, aluminum lake
- Food Yellow No. 4, aluminum lake
- Food Yellow No. 5, aluminum lake

Table 6. Al-containing designated food additives deemed not injurious to human health, related to Articles 12 and 21 of the Food Sanitation Law of Japan (<http://www.tokio.polemb.net/files/Gospodarka/Handel/food-e.pdf>). The conditions of use of all but aluminum potassium sulfate are strictly defined or limited. All lakes are restricted for the purpose of coloring

(including the Food Sanitation Law), under the jurisdiction of the Department of Food Safety under the Pharmaceutical and Food Safety Bureau, in the Ministry of Health, Labour and Welfare. The Standards and Evaluation Division is responsible for the establishment of specifications/standards for food additives. Approved Al-containing food additives are shown in Table 6. The National Standard of the People's Republic of China, Hygiene Standard for Use of Food Additives, GB2760-2007, issued by the Ministry of Health and the Standardization Administration of China, lists the following as allowed food additives: allura, amaranth, brilliant blue, erythrosine, indigo carmine, new red, ponceau 4 r, sunset yellow, and tartrazine aluminum lakes as coloring agents; sodium aluminosilicate as an anticaking agent up to 5 g/kg; aluminum potassium sulfate and aluminum ammonium sulfate as bulking agents and stabilizers with a maximum aluminum residual level of 100 mg/kg dry weight; and starch aluminum octenylsuccinate as a thickener, anticaking agent, and emulsifier (<http://www.fas.usda.gov/GainFiles/200803/146294056.pdf>). Food additives listed by the Bureau of Food Sanitation, Department of Health, Republic of Taiwan, Scope of Usage and Measurement Standards for Food Additives as Food quality improvement, fermentation and food processing agents include aluminum silicate, aluminum sulfate, bentonite, diatomaceous earth, kaolin and sodium silicoaluminate as leavening agents, as well as ammonium alum, burnt ammonium alum, potassium alum, burnt potassium alum, sodium alum, burnt sodium alum, and acidic SALP ([http://www.doh.gov.tw/EN2006/DM/DM2.aspx?now\\_fod\\_list\\_no=6005&class\\_no=386&level\\_no=2](http://www.doh.gov.tw/EN2006/DM/DM2.aspx?now_fod_list_no=6005&class_no=386&level_no=2)). The Government of India Prevention of Food Adulteration Act (PFA) of 1954, enforced by the Food Safety and Standards Authority of India, permits acid compounds of Al in baking powder; aluminum silicates and aluminum ammonium, calcium, potassium or sodium myristates, palmitates or stearates as anticaking agents up to 2%; aluminum sulfate (520) and aluminum sodium sulfate (521) as firming agents; aluminum potassium sulfate (522) as an acidity regulator and stabilizer; aluminum ammonium sulfate (523) as a stabilizer and firming agent; acidic and basic sodium aluminum phosphate (541) as an acidity regulator and emulsifier; sodium (up to 0.5% in powdered soft drink concentrate mix/ fruit beverage drinks and up to 10 gm/kg in cocoa powder and lozenges), potassium and calcium aluminosilicate and aluminum silicate (554, 555, 556 and 559) as anticaking agents; aluminum lake of Sunset Yellow FCF in powdered dry beverage mixes; and aluminum lake of Sunset Yellow and aluminum as colors. The Government of South Africa, Department of Health, Foodstuffs, Cosmetics and Disinfectants Act, 1972, Regulations Relating to Food-Grade Salt, permit calcium, magnesium and sodium aluminum and calcium-aluminum silicates as anticaking agents (<http://www.doh.gov.za/docs/regulations/2006/reg0114.pdf>).

International Numbering System numbers are assigned by the Codex Alimentarius Committee to allow each food additive to be uniquely identified. On packaging in the EC, approved food additives are written with a prefix of 'E'. Some governments, e.g., Australia and New Zealand and India, do not use a prefix letter when listing additives in the ingredients.

#### 4. Al processing and packaging that comes in contact with food

The use of Al cookware began around 1890 (Smith 1928). Al is used in cookware due to its heat conductivity. The surface of Al oxidizes to form a few nm thick layer of Al oxide, which resists corrosion from pH ~ 4.5 to 8.5. Studies on Al mobilization from Al shavings, strips and vessels from 1890 to 1925, reviewed by (Smith 1928), showed Al was solubilized by

beverages and foods. Many subsequent studies have shown that Al can be mobilized from Al cookware, particularly by acidic and alkaline foods. These are pH conditions where Al is more soluble than at circumneutral pH (Fimreite, Hansen, and Pettersen 1997; Scancar, Stibilj, and Milacic 2003; Neelan, Bamji, and Kaladhar 2000; Gramiccioni et al. 1996). It has also been demonstrated that NaCl can increase Al mobilization from Al vessels (Datta 1935; Inoue, Ishiwata, and Yoshihara 1988; Takeda, Kawamura, and Yamada 1998; Fukushima and Tanimura 1998).

Most countries of the world, including the EC, do not have specific requirements for light metal alloys in contact with food (Severus 1989). The conclusion of a review by Wuhler (1939) was that Al is safe and harmless as a material for cooking and household utensils in contact with food. The U.S. FDA came to a similar conclusion (Reilly 1991).

### **5. The contribution of aluminum food additives, processing and packaging to human aluminum intake**

In the UK it was suggested that SALP, sodium Al silicate, and Al lakes contributed ~ 1.4, 0.9 and 3 mg Al to daily intake, respectively (United Kingdom Ministry of Agriculture Fisheries and Food 1993). In the US the two most quantitatively significant food additives containing Al are acidic and basic SALP (Katz et al. 1984; Humphreys and Bolger 1997; Saiyed and Yokel 2005). The use of Al as a food additive can increase the low inherent level of Al in food, particularly in processed cheese and grain products. The foods highest in Al are those with added Al (Delves, Sieniewaska, and Suchak 1993). For example, it was noted that the addition of SALPs to cake mixes could result in 5 to 15 mg/serving and its addition to processed cheese at the permitted concentrations could result in 50 mg Al/slice (Lione 1983). Similarly, the use of sodium Al sulfate in household baking powder could result in 5 mg Al in each serving of a cake made with 1 teaspoon of baking powder (Lione 1983). It has been estimated that this practice can increase food Al content by about five-fold (Humphreys and Bolger 1997).

Women who reported frequent or average use of Al utensils and foil averaged higher duplicate diet Al intakes than those who reported little or no use (Jorhem and Haeggglund 1992). They estimated cooking utensils contributed 2 mg Al to the diet (Jorhem and Haeggglund 1992). Daily Al intake in China was estimated to be 9 to 12 mg plus ~ 4 mg from Al-ware (Wang, Su, and Wang 1994). It was concluded that food processing and storage are generally not major contributors to Al in food (Pennington 1987; Sherlock 1989). Greger and Sutherland (1997) concluded that "... under typical cooking conditions, it is doubtful that use of Al utensils adds more than 2 mg Al/day to food." However, if daily Al intake is 3.5 to 10 mg (see **Daily consumption of Al in food**, below, and Table 1), this would add or constitute about 20 to 40% of the daily Al intake.

### **6. Estimates of the extent of aluminum-containing food additive use**

Estimated use in the 1970s of Al-containing food additives were ~ 18 million kilograms of SALP; 3.6 million kg of sodium Al sulfate in baking powder; and an unknown amount of Na Al silicate, Al calcium silicate and Na calcium aluminosilicate as anticaking agents (FASEB 1975). Based on 200 million people in the U.S. at that time and 10% of SALP as Al, the consumption of 18 million kg SALP/year resulted in an average daily consumption of ~ 25

mg/person/day. The estimate of daily Al consumption at that time was 20 mg/person (FASEB 1975). The 1977 Survey of Industry on the Use of Food Additives estimated use of ~ 9 million pounds (~ 4 million kilograms) of SALP (NAS 1979). The amount of Al in SALP, sodium aluminosilicate, sodium aluminate, aluminum sulfate, and aluminum ammonium sulfate consumed by the 225 million people in the US produced an estimated daily Al intake at that time of ~ 5 mg/person. Al-containing lakes and other sources would increase this estimate. In 1982 four million pounds of Al were used as food additives in the US, which would average 20 mg/person/day (Committee on Food Additives survey data 1984; Greger 1985). Although these estimates are not very consistent over time, they consistently estimate a large amount of Al intake from FDA-approved food additives in relation to total Al intake in the US. More recent estimates of the use of these approved food additives in the US were not found.

Companies in the global phosphates industry that market SALPs include Innophos, which acquired Rhodia's phosphate business in 2004, maker of acidic SALP (Levair®) and basic SALP (Kasal®); ICL Performance Products LP which acquired Astaris LLC in 2005, maker of Levn-Lite®, Stabil-9® and Pan-O-Lite®; Xuzhou Hengxing Chemical Co., Ltd maker of HENGXING®; Amerisweet Co., Ltd. maker of AmeriPhos®; China Chem Source (HK) Co., Ltd.; Foodchem International Corporation; and Thermphos International. Rhodia completed an expansion in 1998 to its Nashville plant to increase its SALP capacity by 15% (Anon, 1998) and Astaris expanded its capacity in 2001 to boost production of SALP.

## 7. Daily consumption of aluminum in food

There have been at least 48 reports that measured or estimated daily oral Al consumption from the diet since the FDA's total diet study reported in 1987. They have been conducted using many different methods, including duplicate portion studies of composite diets, total diet studies, calculations based on the foods in a total diet study times their Al content, and market basket surveys. These studies have been conducted in North America (Canada and the US), Europe (England and the U.K., France, Germany, Hungary, Italy, Netherlands, Portugal, Spain and the Canary Islands, Sweden, and Slovenia), Asia (China, India, Japan, and Taiwan), Australia and Brazil. Median daily Al intake for infants, children, teenagers and adults was 0.7, 6, 8.6 and 4.8 mg, respectively. Total Al intake generally relates to total food intake, which partially explains the greater Al intake in adolescents than adults. Another contributor is the selection of foods. Adolescents eat more prepared foods that have Al-containing food additives. For adults in the US and Canada, Europe, China and Japan, median Al intake by adults was 8.5 (n = 3 reports), 3.6 (n = 18), 9.5 (n = 6), and 9 mg (n = 3), respectively. Al food additives are the main source of Al intake in the US (WHO 1997) but of much less importance in other countries, which includes much of Europe, where less Al is added to cereal grain products as raising agents and basic SALP is not permitted to be used in processed cheese (United Kingdom Ministry of Agriculture Fisheries and Food 1993; Müller, Anke, and Illing-Günther 1998; Sherlock 1989; Humphreys and Bolger 1997). This is reflected in the fewer approved Al food additives and lower minimum permissible levels in the EC than the US (Table 4 compared to Tables 2 and 3). For example, the average Swedish daily diet was calculated to contain ~ 0.6 mg Al from unprocessed foods whereas 105 duplicate diets of 15 women living in the Stockholm area were found to provide 1.2 to 99 mg Al/day, averaging 13 mg Al/day. The most important difference between these was a cake

made from a mix containing Al phosphate (Jorhem and Haeggglund 1992), illustrating the contribution from food additives.

## **8. The aluminum concentration in commercial products that contain aluminum food additives**

Among the three sources of Al in food, naturally occurring, additives and from food preparation and storage, the major food sources of Al in the daily diet of adults ~ 25 years ago were probably grain products with Al additives, processed cheese with Al additives, tea, herbs, spices and salt containing an Al additive (Pennington 1987). It was estimated that grains and grain products, dairy products, desserts, and beverages contributed about 24 to 49%, 17 to 36%, 9 to 26% and 5 to 10%, respectively, of dietary Al in the U.S. diet (Pennington 1987). Similarly, grains, vegetables and tea were estimated to contribute ~ 60 to 70, 25 and 5% of daily Al intake to the Chinese diet (Wang, Su, and Wang 1994; Zhong et al. 1996). The Australian National Nutrition Survey suggested 30, 24, 10 and 8% was from cereals, beverages, vegetables, and meats, respectively (Allen and Cumming 1998). Biego et al. (1998) estimated 36% from milk and dairy products, 29% from fish and crustaceans, 16% from cereals and 8% from vegetables in France. A study from the UK concluded beverages contributed 35%, bread 21%, and cereals 16% of the Al in the diet (Ysart et al. 2000). The Al content of natural cheese and processed cheese containing added Al has been reasonably constant for a few decades. It appears that the use of Al in pancake mixes and prepared pancakes in the US has increased in the past few decades. A report of Al in convenience and fast foods in Spain noted the increased popularity of these foods and considerable Al in them (Lopez et al. 2002).

## **9. Comparison of aluminum intake to established tolerable intake and minimal risk levels**

The Joint Food and Agriculture Organization of the United Nations/World Health Organization Expert Committee on Food Additives (JECFA) withdrew in 2006 its previously established acceptable daily intake (ADI) and provisional tolerable weekly intake (PTWI) of 7 mg/kg body weight to establish a PTWI for Al of 1 mg/kg. It applied to all Al compounds in food, including additives (FAO/WHO 2006; FAO/WHO 2007). The Expert Committee concluded that Al compounds have the potential to affect the reproductive system and developing nervous system at doses lower than those used in establishing the previous PTWI. In setting this limit the Committee assumed a “probable lower bioavailability of the less soluble Al compounds present in food” and noted that the PTWI was likely to be exceeded by some population groups, particularly children, who regularly consume foods containing Al additives. At the 74<sup>th</sup> meeting of the JECFA (June 14 to 23, 2011, Rome) the previous PTWI of 1 mg/kg body weight was withdrawn and a PTWI of 2 mg/kg body weight was established based on a no-observed-adverse-effect level (NOAEL) of 30 mg/kg body weight per day and application of a safety factor of 100. The PTWI applies to all aluminum compounds in food, including food additives ([ftp://ftp.fao.org/ag/agn/jecfa/JECFA\\_74\\_Summary\\_Report\\_4July2011.pdf](ftp://ftp.fao.org/ag/agn/jecfa/JECFA_74_Summary_Report_4July2011.pdf)).

The Panel on Food Additives, Flavourings, Processing Aids and Food Contact Materials (AFC) of the European Food Safety Authority (EFSA) established a tolerable weekly intake

(TWI) of 1 mg Al/kg/week. They also noted that this TWI is likely to be exceeded in a significant part of the European population by the typical dietary Al intake (Panel on Food Additives 2008). Similarly, the Agency for Toxic Substances and Disease Registry (ATSDR) derived an intermediate-duration oral exposure (15 to 364 days) minimal risk level (MRL) of 1 mg Al/kg/day, based on neurodevelopmental effects in the offspring of mice exposed to aluminum lactate in the diet on gestation day 1 through lactation day 21 followed by pup exposure until postnatal day 35 (Golub and Germann 2001).

At the 42<sup>nd</sup> session of the Codex Committee on Food Additives (CCFA) of the Joint FAO/WHO Food Standards Programme (March 15-19, 2010, Beijing, China) it was agreed to establish an electronic working group (eWG) to review comments and information submitted and to revise the maximum use levels for the following Al-containing food additives included in the General Standard for Food Additives (GSFA): acidic and basic SALP, aluminum ammonium sulfate, sodium aluminum silicate, calcium aluminum silicate, and aluminum silicate. The eWG recommended that only numerical maximum levels be set for Al-containing food additives and that they be expressed on an Al basis, and that the potential exposure to Al from the food additive intake be assessed and compared to the PTWI and that proposed levels of Al-containing food additive are not acceptable when the contribution of a single portion of the food with its additive reaches the PTWI. Comments to the draft and the compilation of proposals from the eWG and comments from governments and trade organizations provide further insight into the uses of Al-containing food additives (including the results of a Canadian survey of the maximum levels of use of SALP and sodium aluminum silicate reported by various Canadian food industry stakeholders), and concerns about their safety ([www.cclac.org](http://www.cclac.org)) ([http://www.docstoc.com/docs/80793084/Comments\\_Second\\_Circular\\_Aluminium](http://www.docstoc.com/docs/80793084/Comments_Second_Circular_Aluminium)) ([ftp://ftp.fao.org/Codex/ccfa43/fa43\\_10e.pdf](ftp://ftp.fao.org/Codex/ccfa43/fa43_10e.pdf)). The recommendations of the 43<sup>rd</sup> session of the CCFA (Xiamen, China, March 14 to 18, 2011) were presented to the 34<sup>th</sup> session of the Codex Alimentarius Commission of the Joint FAO/WHO Food Standards Programme (Geneva, Switzerland, July 4 to 9, 2011) ([http://www.cclac.org/documentos/CCFA/2011/1%20Alinorm/REP11\\_FAe.pdf](http://www.cclac.org/documentos/CCFA/2011/1%20Alinorm/REP11_FAe.pdf)). The report of the 34<sup>th</sup> session does not appear to mention these recommendations or whether action was taken on them ([ftp://ftp.fao.org/codex/Reports\\_2011/REP11\\_CACe.pdf](ftp://ftp.fao.org/codex/Reports_2011/REP11_CACe.pdf)).

## **10. The fate of aluminum relevant to its intake by the human in food**

### **10.1 Absorption**

Oral bioavailability (fractional absorption, a.k.a. uptake) is the amount absorbed compared to the amount administered. For Al, systemic bioavailability, the fraction that reaches systemic circulation (blood) from which it has access to the target organs of its toxicity, is most relevant.

Oral <sup>27</sup>Al bioavailability from water from a municipal water treatment facility was estimated to be 0.36% in a study of 21 humans (Stauber et al. 1999). Two studies that had only two human subjects each estimated oral Al bioavailability to be 0.1 and 0.22% (Hohl et al. 1994; Priest et al. 1998). The bioavailability of hydrophilic substances that are not well absorbed can be determined by comparing the area under the curve (AUC) × time for the test substance given orally and intravenously (Rowland and Tozer 1995). Using a modification of this approach the oral Al bioavailability in the rat averaged 0.28% and 0.29% (Yokel et al.



2001a; Zhou, Harris, and Yokel 2008). These studies indicate oral Al bioavailability from water is ~ 0.1 – 0.3%.

Oral Al bioavailability from food has been estimated to be ~ 0.1 to 0.15% based on average daily urinary Al excretion compared to average daily Al intake from food (Powell and Thompson 1993; Priest 1993; Nieboer et al. 1995; Ganrot 1986; Priest 2004). Using the AUC × time method, oral Al bioavailability in rats that ate ~ 1 gm of biscuit containing [<sup>26</sup>Al]-labeled acidic SALP averaged ~ 0.12% (Yokel and Florence 2006) and 0.1% to 0.3% from basic SALP incorporated into cheese (Yokel, Hicks, and Florence 2008). Concurrent consumption of citrate, and to a lesser extent other carboxylic acids, can increase oral Al absorption, as can increased solubility of the Al, a more acidic environment, uremia, and perhaps fluoride (Krewski et al. 2007). Absorption of Al from injected Al in vaccines and allergy immunotherapy is probably completely absorbed over time (Flarend et al. 1997).

Water and food consumption provide ~ 0.1 and 3.5 to 10 mg of Al, respectively, to typical daily Al intake by humans (Table 1). The products of the Al contribution from food and water to the diet × the percentage absorbed (for water 0.1 mg Al consumed daily × 0.3% absorption, delivering 0.3 µg; for food 3.5 to 10 mg Al consumed daily × 0.1% absorption, delivering 7.5 µg of Al to systemic circulation) suggest food provides ~ 25-fold more Al to systemic circulation than does drinking water. This suggests food is the largest single source of Al for the typical human. As food additives are the single largest source of Al in food, they are the greatest contributor to the daily Al intake of the human who is not exposed to other major Al sources (oral antacids, immunization and vaccination injections, occupational exposure and total parenteral nutrition).

## 10.2 Distribution

Normal adult Al content is (in mg/kg wet weight unless stated otherwise): lung: 20, bone: 1 to 3 mg/kg dry weight, liver and spleen: 1, kidney: 0.5, heart: 0.45, muscle: 0.4, brain: 0.35, and blood: 0.002. Approximately 60, 25, 10, 3, 1, 0.3, 0.25 and 0.2% of the Al body burden is in the bone, lung, muscle, liver, brain, heart, kidney and spleen, respectively (Yokel 1997; Priest 2004). Aluminum localizes at the mineralization front and in osteoid of bone. Aluminum in lung may be from environmentally-derived particles, occupational exposure, and distribution from blood. Approximately 80% of an intravenous dose of aluminum citrate was excreted within a week, suggesting the remainder was retained within the body, some of which was excreted over a longer time (Priest et al. 1995). This indicates that Al accumulates in the body during continuous intake, even in subjects with normal renal function. Brain, bone, liver and serum Al concentrations increase with age (Stitch 1957; Zapatero et al. 1995; Markesbery et al. 1984; Roeder and Drasch 1999; Shimizu et al. 1994; Hellström et al. 2005).

The terminal half-life ( $t_{1/2}$ ) of Al has been found to be quite long in the rat and human (reviewed in (Krewski et al. 2007)). The whole-body  $t_{1/2}$  was estimated to be ~50 years in one human who received an intravenous injection of <sup>26</sup>Al citrate, based on whole-body <sup>26</sup>Al monitoring (Priest 2004). The  $t_{1/2}$  of Al in the rat brain has been estimated to be from ~ 150 days to considerably greater (Yokel et al., 2001b; Yumoto et al., 2003). The lack of a good understanding of allometric scaling of metal elimination rates for rat to human make it difficult to predict the human brain Al  $t_{1/2}$ . Given the large percentage of Al in bone, it probably drives the Al concentration and elimination  $t_{1/2}$  throughout the body.

### 10.3 Biotransformation

Aluminum associates avidly with transferrin in the blood, which binds > 90 of Al in the blood. In the cerebrospinal fluid, and presumably brain extracellular fluid, ~90 of the Al is believed to be associated with citrate (calculated by Dr. Wesley Harris; Yokel and McNamara 2001).

### 10.4 Excretion

The kidneys account for > 95% of Al excretion, presumably by glomerular filtration of aluminum citrate. Humans who daily consume 3.5 to 10 mg of Al would be expected to excrete 4 to 12 µg, generating a typical urinary Al concentration of 2 to 10 µg/L. Reduced or absent renal function creates the risk of Al accumulation and toxicity. The biliary route accounts for most of the remaining excreted Al.

## 11. The most susceptible population to aluminum toxicity

Those who have impaired or no renal function are at the greater risk of Al toxicity because of their reduced ability to excrete it. In a study, patients with chronic renal insufficiency who used Al kitchen utensils for > 1 year were divided into two groups, one that continued to do so for 3 months; the other used stainless steel utensils. The latter group showed a significantly greater decrease in serum Al and daily urine Al excretion. These results suggest Al kitchen utensils may be a significant Al source for this population (Lin et al. 1997). When foods provide more Al in the diet than cookware, as is usually the case, one might expect foods that contain considerable Al to have an even greater contribution to the Al body burden of patients with chronic renal insufficiency than produced by Al kitchen utensils.

## 12. The primary known adverse health effects of aluminum in the human

There is no good evidence that Al is essential or beneficial for the human. Aluminum can produce toxicity to the central nervous, skeletal and hematopoietic systems. It can produce an encephalopathy in renal-impaired humans (dialysis encephalopathy), cognitive deficits in young children, a low-turnover bone disease, a microcytic hypochromic anemia, and has been implicated as an environmental factor that may contribute to some neurodegenerative diseases, including Alzheimer's disease.

The toxicity of Al has been extensively reviewed by the World Health Organization, for the US Department of Health and Human Services, and most extensively by a multi-national group led by Daniel Krewski (WHO 1997; ATSDR 2008; Krewski et al. 2007). When hemodialysis was initially extensively used, some patients developed a progressive encephalopathy that was fatal within 6 months. Dialysis (associated) encephalopathy (aka: dialysis dementia) is characterized by dyspraxia, dysarthria, emotional changes, trembling, ataxia, myoclonus, and fatal convulsions. It is associated with elevated levels of Al in the brain, and serum Al > 80 µg/L (Nieboer et al. 1995). Dialysis encephalopathy was due to Al contamination of the dialysis fluids and administration of Al-based phosphate binders to form an insoluble Al phosphate in the intestine, facilitating phosphate elimination, a goal not well achieved by dialysis. The renal dialysis patient is highly susceptible to Al accumulation and toxicity from Al in dialysis fluids because the Al can diffuse across the dialysis membrane, it rapidly and very strongly binds to transferrin in the blood, and these

patients lack the primary route of Al elimination, renal function. Exposure to lower levels of Al than those that caused Al-induced encephalopathy can produce a low turnover bone disease and a microcytic anemia.

### **12.1 Aluminum-induced bone disease**

Aluminum-induced low-turnover bone disease is manifest as osteomalacia and an adynamic bone disease (Bushinsky 1997). Aluminum-induced bone disease in dialysis patients is seen when serum Al is  $> 30 \mu\text{g/L}$  and when stains show Al at 30% of the trabecular bone surface (Landeghem et al. 1998; Malluche and Monier-Faugere 1994).

### **12.2 Aluminum-Induced microcytic anemia**

A microcytic, hypochromic anemia is associated with elevated plasma Al in chronic renal failure patients (Jeffery et al. 1996).

### **12.3 Evidence for and against a role of aluminum in Alzheimer's Disease**

Aluminum has been implicated in the etiology of Alzheimer's disease (AD) (Kawahara 2005; Spencer 2000; Gupta et al. 2005; Krewski et al. 2007; Bondy 2010; Tomljenovic 2011). Hallmark neuropathological signs include neurofibrillary tangles (NFTs), senile plaques (SP), and cerebrovascular amyloid. Early onset AD usually has a familial link, due to gene mutations which result in increased secretion of neurotoxic amyloid  $\beta$  protein ( $A\beta$ ). No specific gene mutations have been associated with late-onset/sporadic forms of AD which account for 85 to 95% of AD cases. The lack of identified hereditary links for the majority of AD cases suggests environmental factors are likely to interact with other factors to cause this disease. Aluminum is one of the suggested environmental contributors. The genesis of the hypothesis that Al plays a role in the etiology of AD was an observation reported in 1965 of neurofibrillary degeneration in rabbit brain after intracerebral Al injection, which resembled, but was not identical to, the NFTs of AD (Klatzo, Wisniewski, and Streicher 1965). Similarly, the neuropathology in dialysis encephalopathy is different from that seen in AD. The observation of elevated Al in post-mortem brain samples (that typically weighed scores of milligrams) of humans with AD reported in 1973 was interpreted as suggesting a role for Al in AD (Crapper, Krishnan, and Dalton 1973). This was followed by many studies, some of which found a few-fold or smaller increase of the Al concentration in AD victim brains than in controls, and some which did not. Studies investigating an elevated level of Al in AD brain using microprobe techniques, such as energy dispersive (electron probe) X-ray microanalysis, secondary ion mass spectrometry, and laser microprobe mass spectroscopy which can quantify Al within a cell, NFT or SP, as well as Al-selective stains, have also produced mixed results (Yokel 2000). If Al is elevated in AD brain, it is not reflected in cerebrospinal fluid Al, which has generally not been found to be elevated (Kapaki et al. 1993). Even if Al is elevated in AD brain, it does not prove cause and effect. The neuronal degeneration of AD may result in accumulation of metals, such as Al.

Another approach to address the potential role of Al in AD is the epidemiological study of the association between the concentration of Al in drinking water and AD incidence, comparing geographic regions where drinking water Al concentrations differ. Again, the

results of many such studies are not consistent. The majority reported an increased risk of AD associated with higher drinking water Al concentration. Some of the differences were statistically significant. A major review published in 2007 conducted a risk characterization of the route of Al intake, the exposure level of concern, and Al exposure in the general population and calculated a margin of exposure (ratio of the exposure level of concern to the exposure level) (Krewski et al. 2007). The exposure level of concern was based on an epidemiological study that showed a relative risk of AD of 2.14 associated with a drinking water Al concentration  $> 100 \mu\text{g/L}$  (Rondeau et al. 2000).

Given that Al bioavailability from water is not considerably greater than from food, studies assessing a putative link between Al in drinking water and AD might be mis-focused, and studies investigating a possible association between Al in food and cognitive impairment, dementia and AD might be more relevant. However, these are much more difficult to conduct, due to the multiple sources of Al in foods. It has been stated by US FDA employees that no clinical syndrome has been noted for the very low intake of dietary Al (Humphreys and Bolger 1997). It was also suggested that the risk of adverse effects of dietary Al, if there are any, is extremely low (Soni et al. 2001). The only published study addressing the potential association between Al in food and dementia was a preliminary study of 23 newly-diagnosed AD patients and 23 matched non-demented controls to ascertain the relationship between consumption of foods generally high in Al during the previous 5 years and dementia. The results showed increased odds ratios for many food categories. However, the results were only significant for the category containing pancakes, waffles, biscuits, muffins, cornbread and corn tortillas (Rogers and Simon 1999).

### **13. Determination of aluminum body burden and its treatment**

Determination of elevated body burden of Al might be made by quantification of Al in blood. However, this is quite difficult because the blood Al concentration of the normal healthy human is very low, thought to be  $< 6 \mu\text{g/ml}$ , and probably  $\sim 2 \mu\text{g/ml}$  (Daniela et al. 2002; House 1992; Valkonen and Aitio 1997), and due to its ubiquitous nature, sample contamination is very easily obtained. The desferrioxamine test, a single injection of 5 mg/kg this chelator, has been used to assess Al body burden, as evidenced by an increase in serum Al and urinary Al clearance. The test dose is used because steady-state serum Al concentrations do not correlate well with the Al deposition in bone and soft tissues that results from long-term Al exposure (Yokel 2002; Seo et al. 2007). Up to 5 mg/kg of desferrioxamine once or twice weekly has been shown to be safe and effective for long-term treatment of Al overload, and reduction of Al-induced encephalopathy, bone disease and anemia (Kan et al. 2010).

### **14. Aluminum toxicity in the premature infant**

Another high risk group for Al toxicity is premature infants who are fed intravenously, because they do not tolerate oral feeding. The total parenteral nutrition feeding solutions given intravenously can contain significant Al, which is primarily derived from the calcium gluconate and phosphates used as components of the solution. As this feeding solution is given intravenously, and therefore 100% bioavailable, to premature infants whose kidneys are not fully matured and therefore less able to excrete the Al, they are at risk of sufficient Al

accumulation to develop metabolic bone disease, cholestatic hepatitis, and reduction of mental development. To address this concern the U.S. Food and Drug Administration adopted a labeling requirement for Al in large and small volume parenterals used to prepare total parenteral nutrition solutions. This has not solved the problem.

## 15. Summary

For the typical human, food additives provide the largest source of daily Al intake, exceeding water by several orders of magnitude, the latter having been implicated as a contributing factor to dementia, specifically Alzheimer's disease. The food additive contributing the greatest amount of Al to the diet is SALP, used in its acidic form as a leavening agent in baked goods and in its basic form as an emulsifying agent in cheese. Acidic SALP is an approved food additive in most countries. Basic SALP is approved for use in many fewer countries. There has been debate for a century about the safety of Al as a food additive. This debate continues, and is reflected in recently changed established tolerable intake and minimal risk levels and changes under consideration. It has been noted that there is no good evidence of adverse health effects attributed to Al from food, that this issue has not been adequately directly assessed, and that those who lack good renal function, and therefore unable to efficiently eliminate Al, are at greatest risk of Al-induced toxicity, perhaps from food. As with the controversy concerning a possible role of Al in the etiology of Alzheimer's disease, the controversy about possible adverse effects of Al as a food additive will continue until more definitive demonstration of safety or untoward effect is demonstrated.

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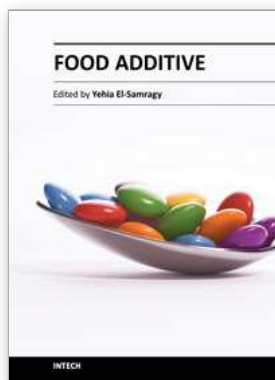
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## **Food Additive**

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A food additive is defined as a substance not normally consumed as a food in itself and not normally used as a characteristic ingredient of food whether or not it has nutritive value. Food additives are natural or manufactured substances, which are added to food to restore colors lost during processing. They provide sweetness, prevent deterioration during storage and guard against food poisoning (preservatives). This book provides a review of traditional and non-traditional food preservation approaches and ingredients used as food additives. It also provides detailed knowledge for the evaluation of the agro-industrial wastes based on their great potential for the production of industrially relevant food additives. Furthermore the assessment of potential reproductive and developmental toxicity perspectives of some newly synthesized food additives on market has been covered. Finally, the identification of the areas relevant for future research has been pointed out indicating that there is more and more information needed to explore the possibility of the implementation of some other materials to be used as food additives.

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University Campus STeP Ri  
Slavka Krautzeka 83/A  
51000 Rijeka, Croatia  
Phone: +385 (51) 770 447  
Fax: +385 (51) 686 166  
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### **InTech China**

Unit 405, Office Block, Hotel Equatorial Shanghai  
No.65, Yan An Road (West), Shanghai, 200040, China  
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元  
Phone: +86-21-62489820  
Fax: +86-21-62489821